IMMUNOSUPPRESSION

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MAIN TOPICS

I- Introduction

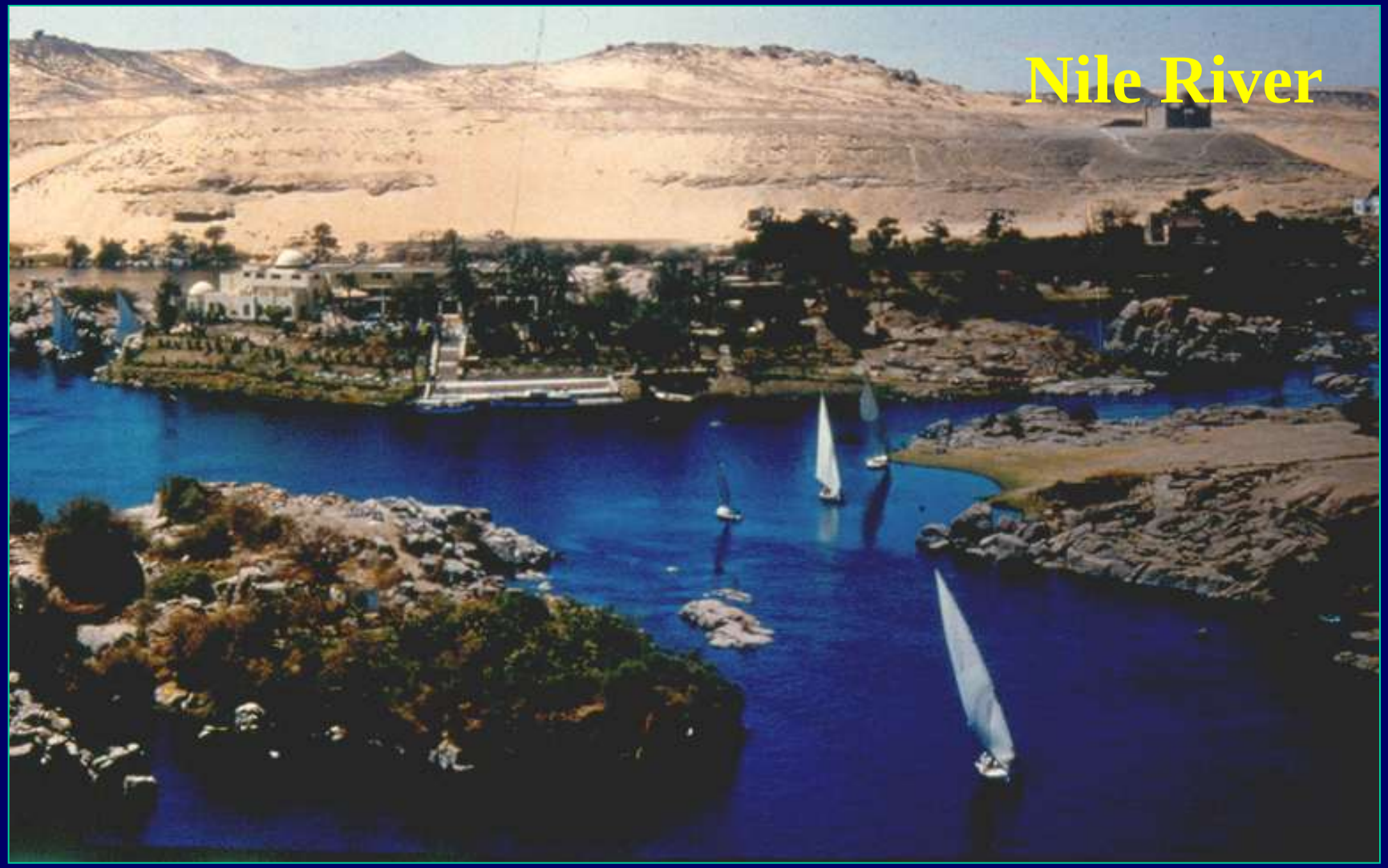
II- Mechanism Of Action

III- Drug Interactions

IV- Trends

V- At The End

Immunosuppression



I. Introduction

I. Introduction

- **Over the last 15 years, immunosuppressive regimens have changed significantly.**
- **The number of agents available for induction and maintenance therapies have greatly increased.**

I. Introduction: Types

I- Glucocorticoids.

II- Small-molecule drugs:

a) Immunophilin-binding drugs:

- Calcineurin inhibitors:

*** Cyclophilin-binding drugs: cyclosporine.**

*** FKB12-binding drugs: Tacrolimus.**

- mTOR Inhibitors: SIR, EVR.

(Pellegrino, Medscape, 2013)

I. Introduction: Types

II- Small-molecule drugs

b) Inhibitors of nucleotide synthesis:

- Purine synthesis (IMDH) inhibitors:

* **Mycophenolate mofetil.**
* **Enteric-coated mycophenolic acid (EC-MFS).**
* **Mizoribine (MZR).**

(Pellegrino, Medscape, 2013)

I. Introduction: Types

II- Small-molecule drugs:

c) Pyrimidine synthesis (DHODH) inhibitors:

- **FK778.**
- **Leflunomide.**
- **Antimetabolites: Azathioprine.**
- **Sphingosine-1-phosphate-receptor antagonists: FTY720.**

(Pellegrino, Medscape, 2013)

I. Introduction: Types

III- Protein drugs

a) Depleting antibodies (against T or B cells, or both):

- **Polyclonal antibody: horse or rabbit antithymocyte globulin.**
- **Mouse monodonal anti-CD3 antibody (muromonab-CD3).**
- **B-cell-depleting monoclonal anti-CD-20 antibody (rituximab).**

(Pellegrino, Medscape, 2013)

I. Introduction: Types

III- Protein drugs:

b) Nondepleting antibodies and fusion proteins:

- **Humanized or chimeric monoclonal anti-CD25 antibody.**
- **Fusion protein with natural binding properties:**

  *** CTLA4-1g (Belatacept).**

(Pellegrino, Medscape, 2013)

I. Introduction: Types

IV- Intravenous gammaglobulin: IVIG

V- C5 inhibitor: : Eculizumab.

VI- Protease inhibitor: : Bortezomib.

(Pellegrino, Medscape, 2013)

Immunosuppression

II. Mechanism Of Action

II. Mechanism of action

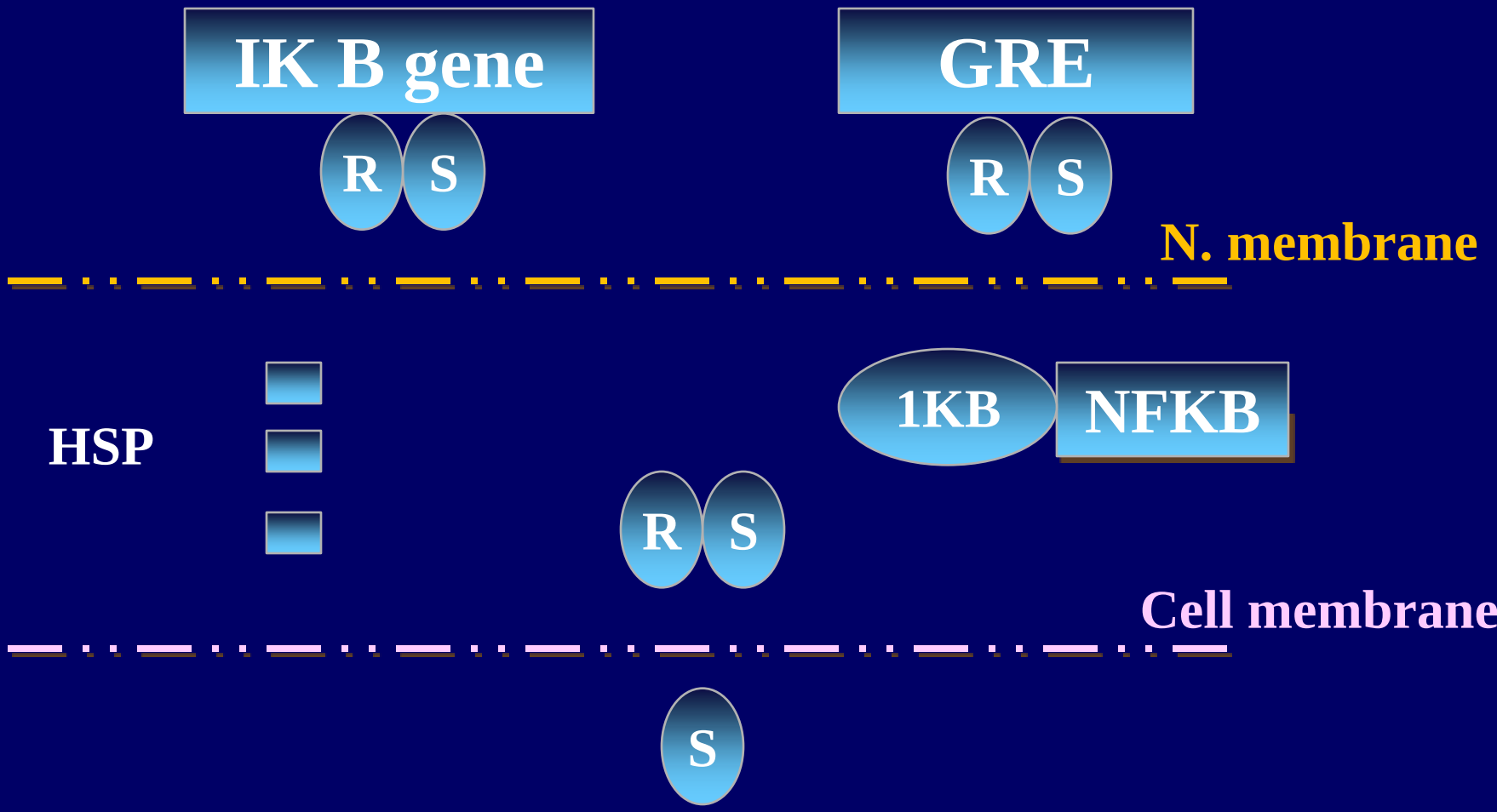
❑ Glucocorticoids:

- **Complex pharmacology.**
- **For induction, maintenance and antirejection.**
- **Prevents production of cytokines, TNFα, IL2, 6, chemokines, prostaglandins, MHC class II and proteases.**
- **Affect phagocytes and B cells.**

(Halloran et al., NEJM, 2004)

II. Mechanism of action

❑ Steroid



II. Mechanism of action

❑ Azathioprine:

- **Inhibitis both DNA and RNA synthesis.**
- **Blocks the production of IL2 in MLR.**
- **Affects cell mediated and humoral immunity.**
- **Metabolites excreted in urine (inactive).**
- **Cross placenta with no significant malformation.**
- **Concomitant administration of allopurinol:**
  - **4 folds increase immunosuppression.**
  - **2 folds increase hematologic toxicity.**

(Cristelli et al., Transpl Infect Dis, 2013)

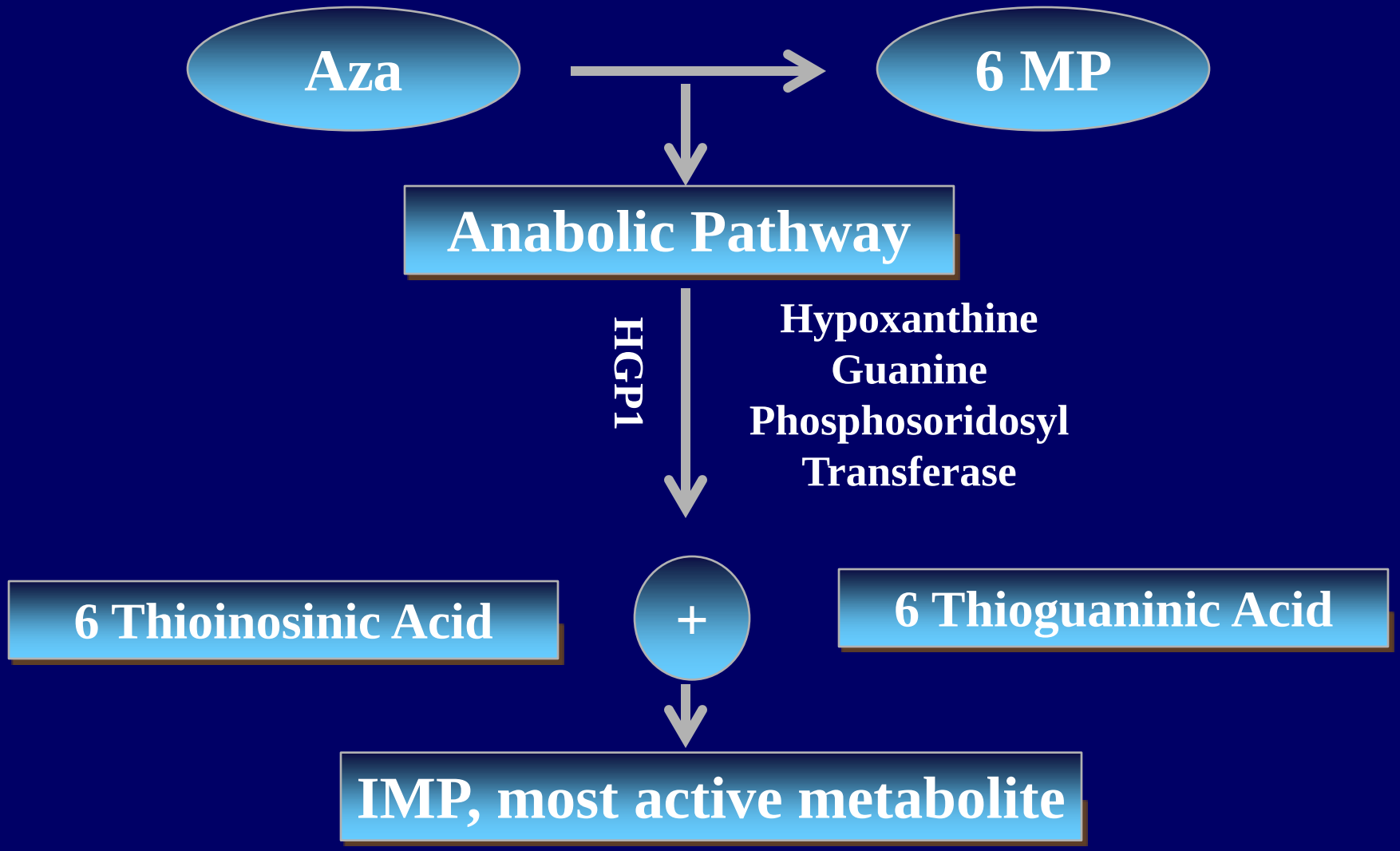
II. Mechanismof action

❑ Azathioprine:

- **Cheap.**
- **Selective conversion from MPA to Aza after one year is safe even in high risk renal transplant patients.**
- **Still a viable option for low risk renal transplant patients receiving Tac and P.**

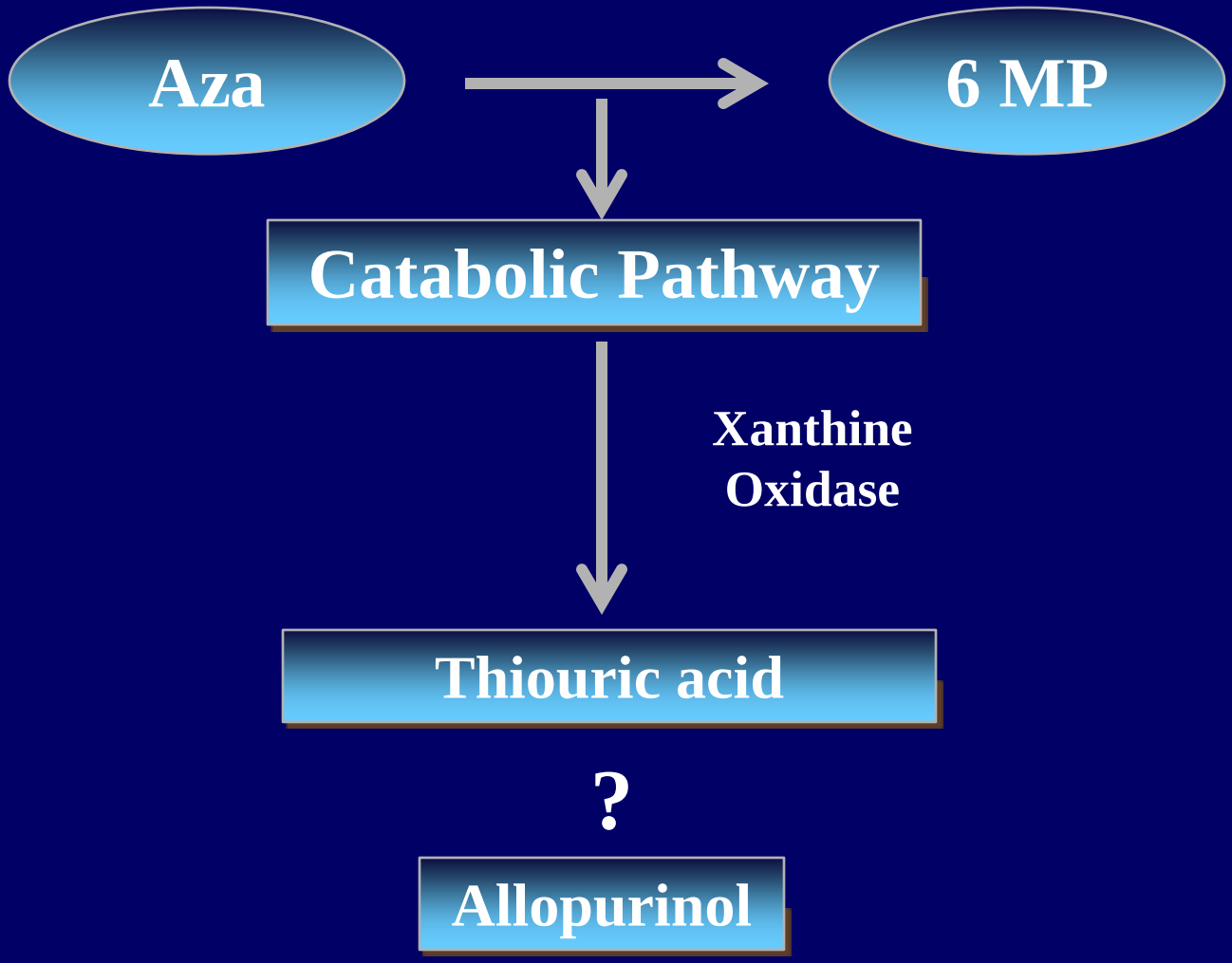
(Cristelli et al., Transpl Infect Dis, 2013)

II. Mechanism of action



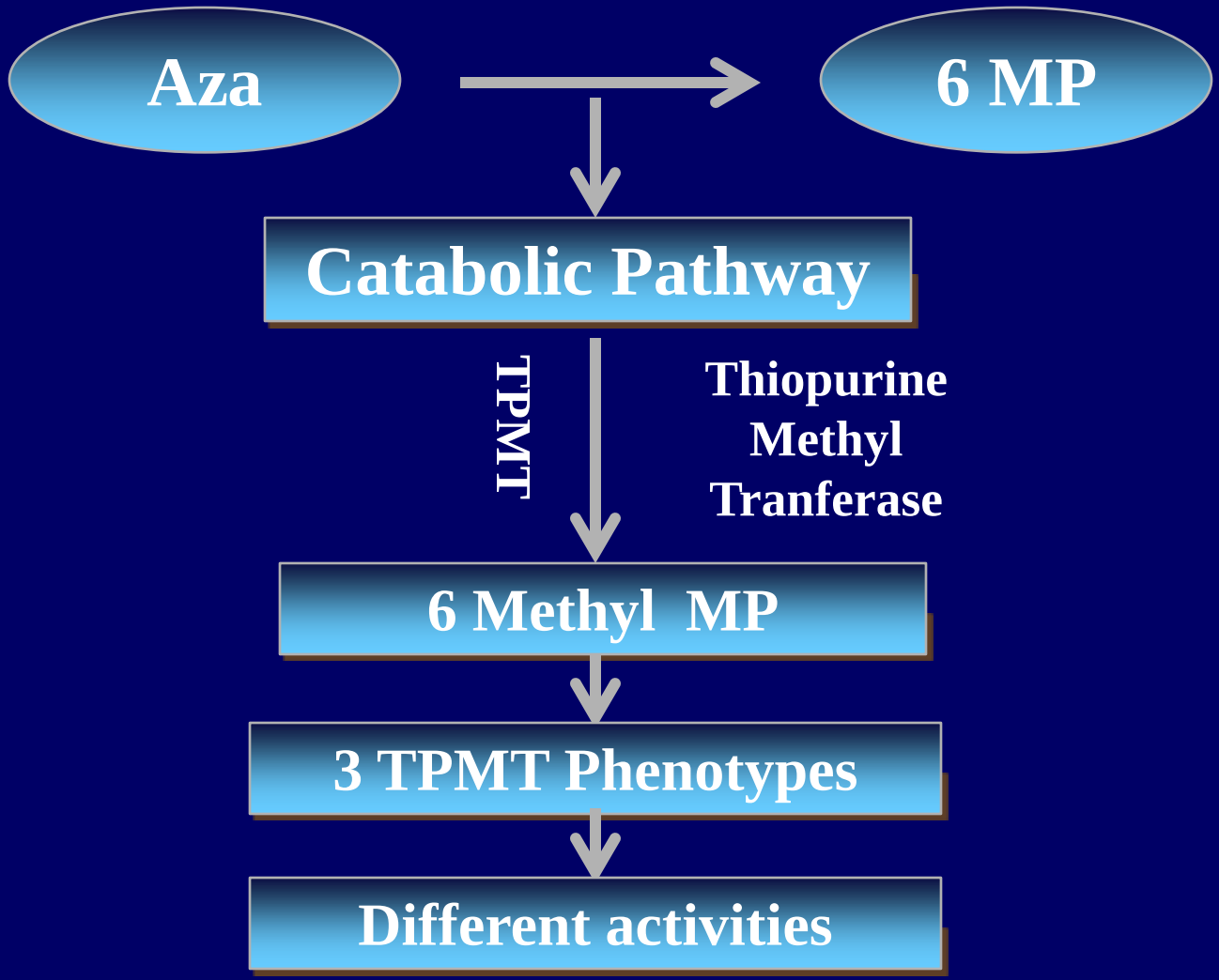
(Dervieux et al., Br J Clin Pharmacol, 1999)

II. Mechanism of action



(Dervieux et al., Br J Clin Pharmacol, 1999)

II. Mechanism of action



(Dervieux et al., Br J Clin Pharmacol, 1999)

II. Mechanism of action

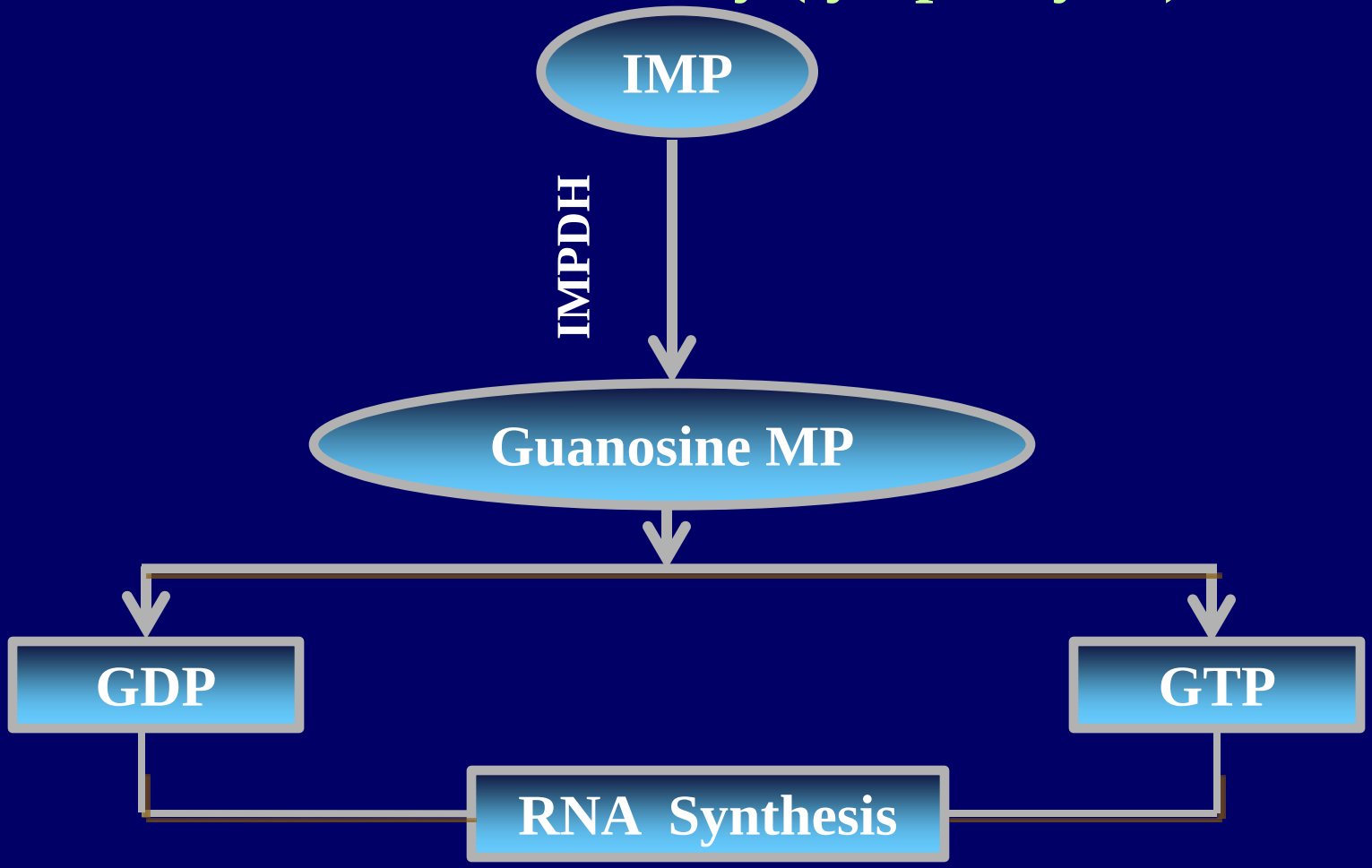
❑ MPA:

- **Inhibits de novo purine synthesis.**
- **Potent, selective inhibitor of IMPDH.**
- **Potent cytostatic effect on lymphocytes.**
- **Selectively inhibits B, T cell proliferation.**
- **No effect on cytokines associated with early T cell signal transduction (IL1,2).**
- **Inhibits arterial smooth muscle, fibroblast and endothelial cell proliferation.**

(Ting et al., Ther Drug Monit,2008)

Mechanism of action :MPA

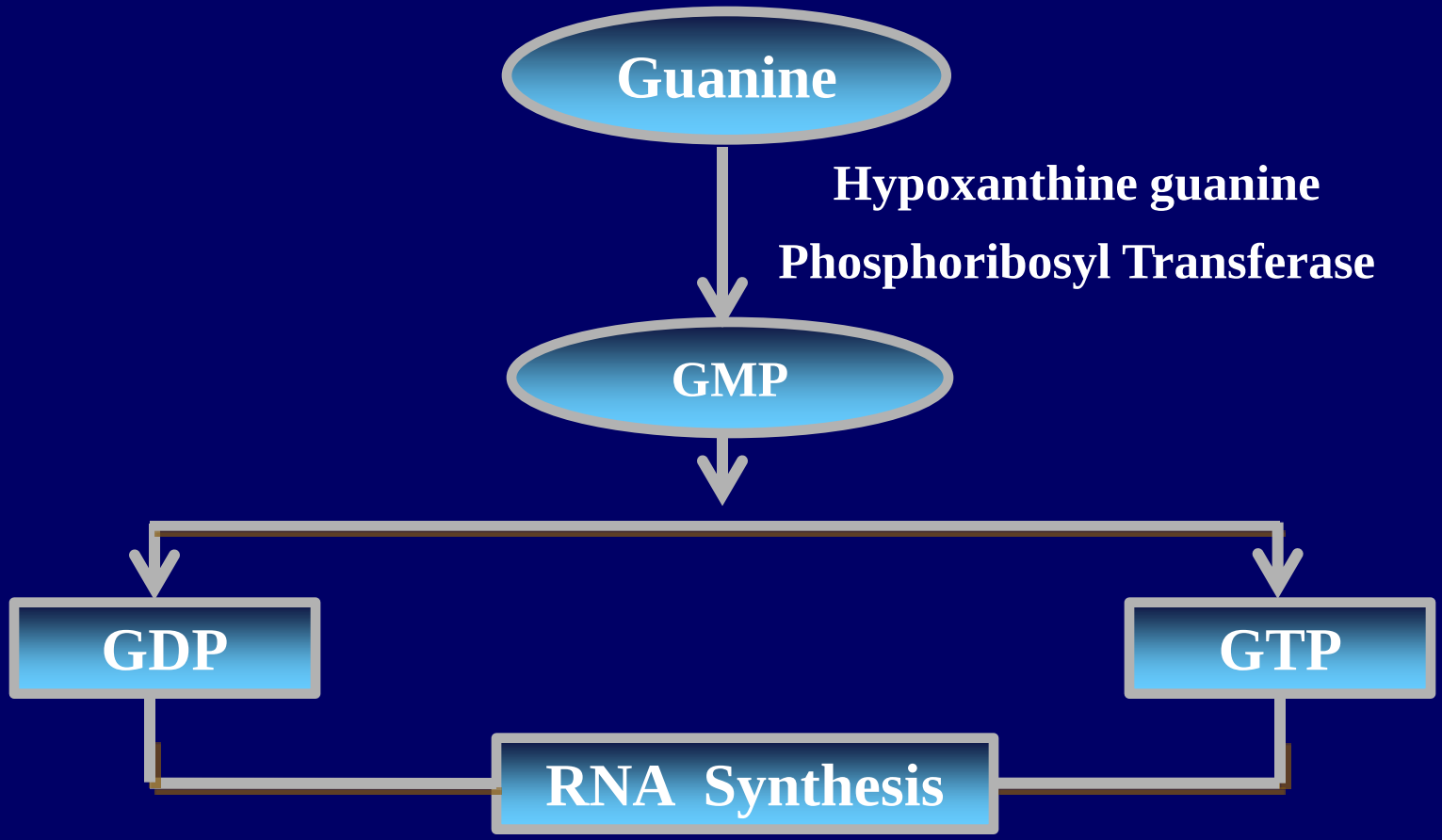
Denovo Pathway (lymphocytes)



(Ronsom, Ther Drug Monit, 1995)

Mechanism of action :MPA

Salvage Pathway (Mammalian cell)



(Ronsom, Ther Drug Monit, 1995)

II. Mechanism of action

- **Antithymphocytic Globulin:**
  - **Decreases number of T cells.**
  - **Decreases proliferative function.**
  - **After treatment:**
    - **Number increases.**
    - **Proliferation remained impaired.**

(Gharekhani et al., Expert Opin Biol Ther, 2013)

II. Mechanism of action

❑ Anti CD25:

- **Inhibits IL2 mediated activation of the lymphocytes (important for clonal expansion of T cells).**
- **High affinity to alpha subunit of IL2R (CD25).**

(Raminez et al., Unit Biol Ther, 2001)

II. Mechanism of action

❑ CNlS: Cyclosporine :

- **Complete inhibition of ML Reaction.**
- **Significant inhibition of IL2 production.**
- **Inhibits the generation of cytotoxic T cells.**
- **Inhibits IL1, IL3 and gamma interferon.**
- **Inhibits induction of class II antigen expression.**
- **Blocks the prolactin binding to its receptors.**

(Llaudo et al., Transpl Int, 2013)

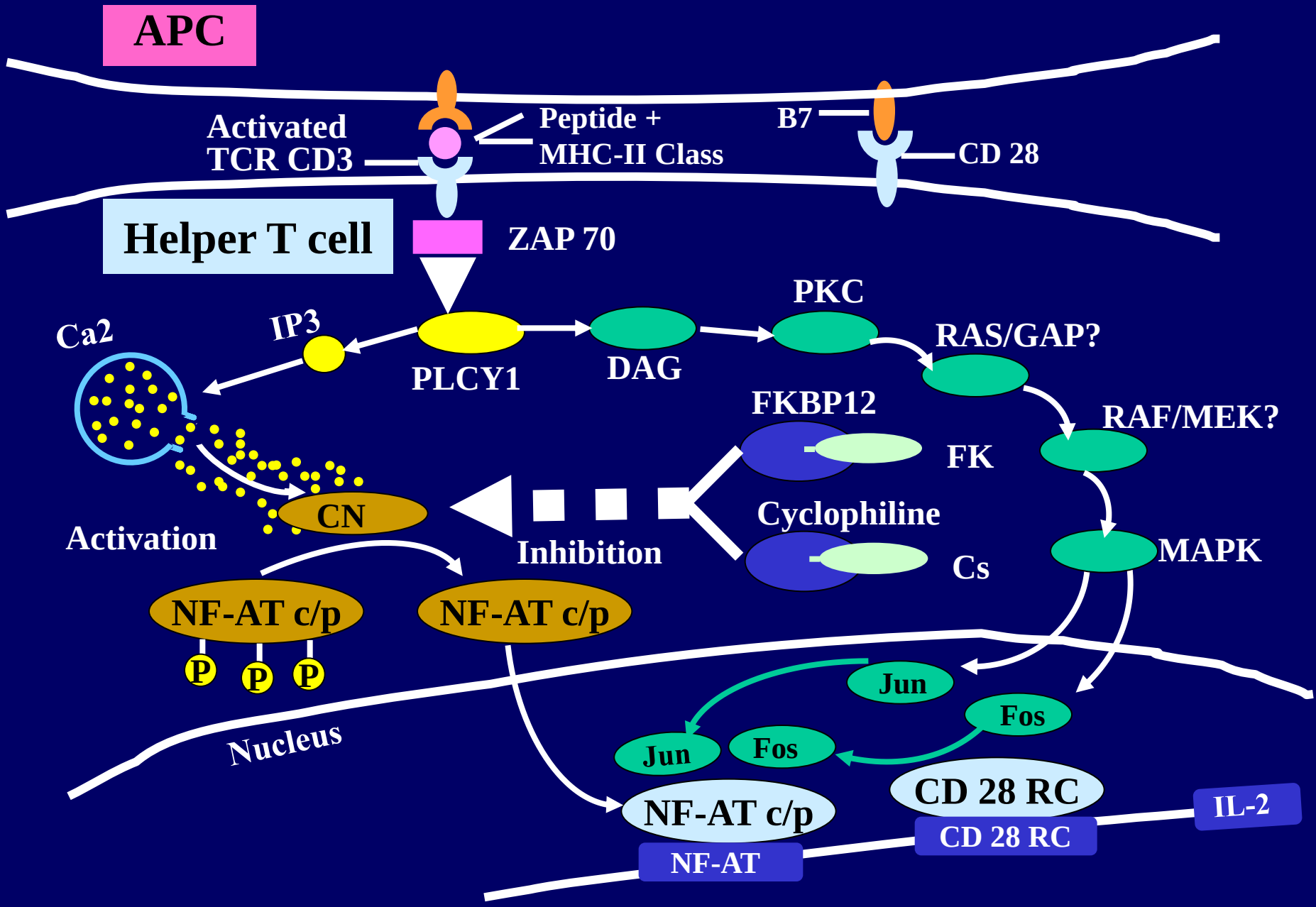
II. Mechanism of action

❑CNIs: Tac:

- **Most frequent CNI used currently.**
- **Main metabolic pathway is cytochrome P450 (CYP3A).**
- **Drug interactions as CsA.**
- **T cell specific CNI.**

(Kamdem et al., Clin Chem, 2009)

Immunosuppression: CNIs



II. Mechanism of action

- **mTOR:**
  - **Inhibits, IL2, 4, 5, 6,7 and 15.**
  - **Blocks cell cycle progression at G1 phase.**
  - **Inhibits proliferation of B and T lymphocytes.**
  - **Decreases IgG, IgM, IgA production through inhibiting IL6 effect on antibiody producing cells.**

(Shah et al., Transplanation, 2012)

II. Mechanism of action

❑mTOR:

- **Deceases Cyclic AMP induced late gene transcription.**
- **Inhibits one or more phosphatases or kinases.**
- **Limited effects on cytokine production.**

(Shah et al., Transplanation, 2012)

II. Mechanismof action

❑ Mizoribine:

- **Inhibits IMDH.**
- **Depleting guanine rihonucleotides.**
- **Selective inhibitation of T lymphocyte proliferation.**
- **Used in Japan and not approved in North America.**
- **Similar efficacy and safety to MPA combined with Tac.**
- **Significantly high uric acid levels.**

(Ju et al., Transplant Proc, 2013)

II. Mechanism of action

❑Leflunomide:

- **Has immunosuppressive and antiviral proporties.**
- **Used in resistant CMV, BKVN, renal transplant with CAD.**
- **May provide to eradicate CMV, BK.**
- **Not recommended as first line agent instead of MPA, SIR.**

(Chon and Josepson, Expert Rev Clin Immunol, 2011)

II. Mechanism of action

- **Belatacept:**
  - **Fusion protein binds B_7 molecule on the surface of APC.**
  - **Costimulation blockade of CD_{28}- B_7.**
  - **Inhibitis cell mediated and humoral immune response in vivo.**

(Vincents et al., NE J M, 2005)

Immunosuppression

III. Drug Interactions

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A) Pharmacokinetic interaction:

Drug alters

↓

Absorption
Distribution
Metabolism
Elimination

↓

Of another drug

III. Drug Interactions

A) Pharmacokinetic interaction:

Drug alters

Absorption
Distribution
Metabolism
Elimination

Of another drug

III. Drug Interactions

- **Gut metabolism.**
- **Alteration in active transport.**
- **Changes in intestinal motility.**
- **Chelation.**

(Gelone et al., Pharmacotherapy, 2007)

III. Drug Interactions

A) Pharmacokinetic interaction:

Drug alters

Absorption
Distribution
Metabolism
Elimination

Of another drug

III. Drug Interactions

- **Drugs with high protein bound.**
- **Drug can be displaced from its binding site by another drug with greater affinity to that site .**
- **Raise the free concentration of displaced drug.**
- **MPA with 97% bound to albumin as example**
- **Clinical relevance is minor**

(Lynch and Price, Am Fam Physicians 2007)

III. Drug Interactions

A) Pharmacokinetic interaction:

Drug alters

↓

Absorption
Distribution
Metabolism
Elimination

↓

Of another drug

III. Drug Interactions

- **Drug becomes more water soluble that can be more easily eliminated.**
- **CsA, Tac and SIR are substrates of CYP3A isoenzyane system.**
- **There are inhibitory or inducing interactions.**
- **Allopurinol – Aza interaction is not mediated through CYP.**

(Baroletti et al., Prog Transplant, 2004)

III. Drug Interactions

A) Pharmacokinetic interaction:

Drug alters

↓

Absorption
Distribution
Metabolism
Elimination

↓

Of another drug

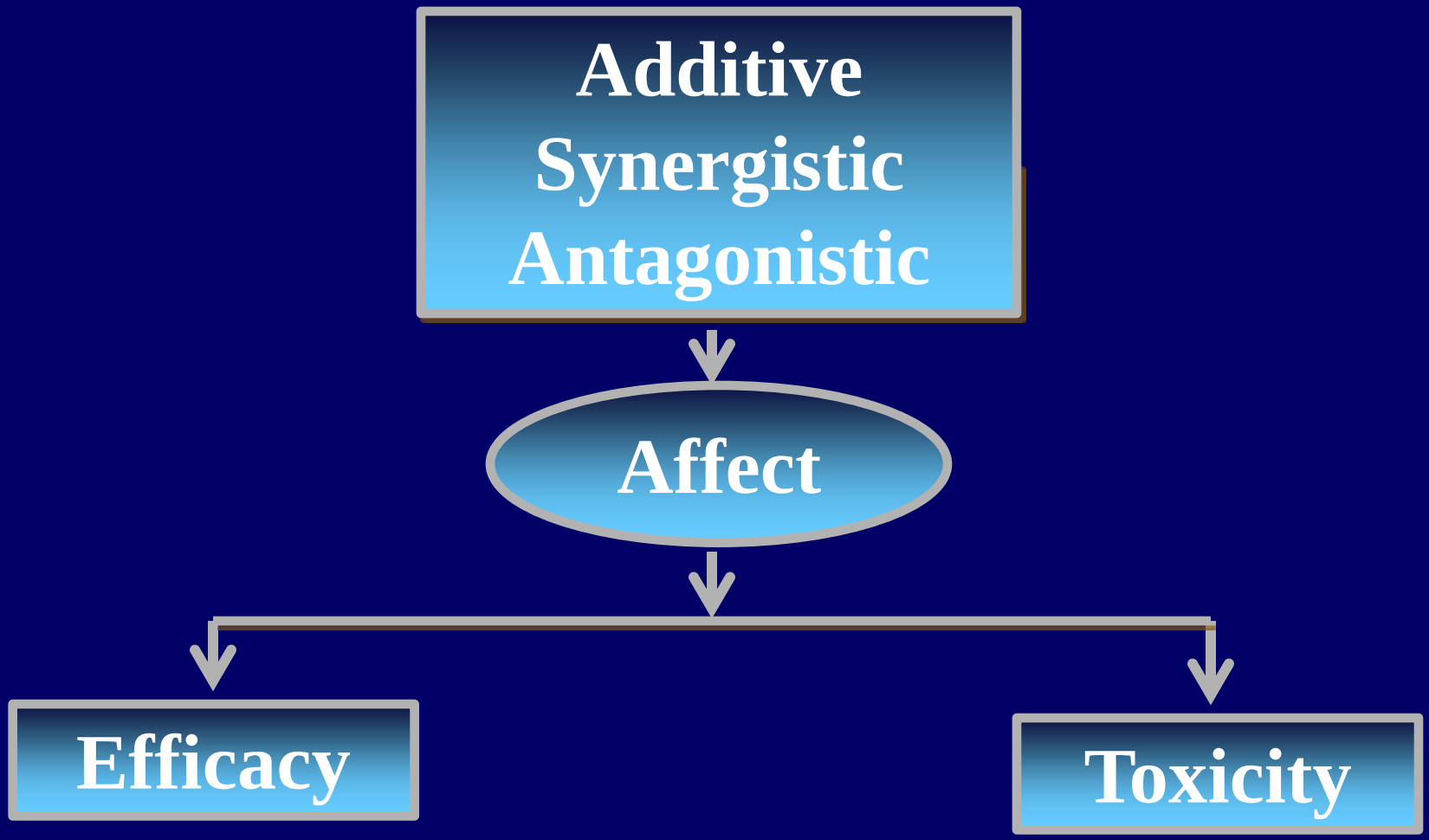
III. Drug Interactions

- **Few interactions**
- **Major interaction example involves MPA**
- **Several medications interfere with biliary excretion of MPA glucuronide eliminating reabsorption and lowering overall exposure.**

(Gabardi et al., Ann Pharmacother, 2003)

III. Drug Interactions

B) Pharmacodynamic interaction:



III. Drug Interactions

b) Pharmacodynamic interaction:

- **Common when multiple drugs are utilized with different modes of actions.**
- **May be problematic when drugs with similar adverse events are used concomitantly.**
- **Examples aminoghycoside, Amphotericin B and NSAID .**
- **Potentiate nephrotaxicity of CNIs**

(Gabardi et al., Ann Pharmacother, 2003)

Immunosuppression

IV. Trends

Immunosupperssion Rings of the chain

Conventional Vs Cyclosporin
RING I
AM J Nephrol, 13, 437: 1993

Transform
RING X
?

Avoidance
RING IX
In Press

Triple Vs Conventional
RING II
Transplant Proc., 25: 2243: 1993

Steroid Free
RING VIII
Exp Clin Tx, 5:673, 2009

Cyclosporine Neoral
RING III
Transplant Proc., 29(7): 2939: 1997

mTOR
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JASN, 19:1225, 2008

Keto Vs non Ketoconazole
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RING X
Transform
?

IV- Trends

Ring I

Prospective Randomized Study Of Azathioprine Versus Cyclosporine In living Donors Kidney Transplantation.

- **No. of patients : 112.**
- **GI : 54 recipients : P +Aza.**
- **GII : 58 recipients : P +CsA.**
- **Follow up Range : 3-6 Years**
  Mean : 50 ± 8 M

(Mansoura Team, Am J Nephrol , 1993 ;13 (6): 437)

IV- Trends

Ring I

- ***No significant difference in:***
  - **Graft survival.**
  - **Patient survival.**
  - **Overall frequency of AR.**
- ***But higher:***
  - **S. creatinine at 1, 12, 24 M. in GII.**
  - **Number of patients had ≥ 2 AR in GI.**

(Mansoura Team, Am J Nephrol , 1993; 13 (6): 437)

IV- Trends

Ring I

- ***Results at 15 years:***
  - *Comparable graft survival.*
  - *No difference in:*
    - *Graft function.*
    - *Rejection frequency.*
    - *Malignancy.*
    - *Hepatic dysfunction.*

(Mansoura Team, Saudi J Kidney Dis Transpl, 2008; 19(4): 564)

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Transplant Proc., 26(6): 316: 1994

RING V
Rescue therapy: FK and MMF
Exp Clin Tx, 6: 48, 2008

RING VI
Induction therapy With simulect
J Nephrol, 2003

IV- Trends

Ring II

Prospective Randomized Study Of Triple Vs Conventional Immunosuppression In living Donors Kidney Transplantation.

- **No. of patients: 100.**
- **Group I : P +Aza + CsA.**
- **Group II : P +Aza.**
- **Follow up :**
  - **Range 20-43 M.**
  - **Mean 32±10 M.**

(Mansoura Team, Transplant Proc , 1993; 25 (3) : 2243)

IV- Trends

Ring II

- ***No significant difference in:***
  - **Patient and graft survival at 1, 3Y.**
  - **S. Creatinine along follow up period.**
  - **Frequency of acute rejection.**
  - **Post transplant complications:**
    - **HTN, DM.**
    - **Kaposi's sarcoma.**
    - **Chronic rejection/IFTA.**

(Mansoura Team, Transplant Proc , 1993; 25 (3) : 2243)

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IV- Trends and Trials

Ring III

Cyclosporine Neoral In Renal Transplant Recipients: Impact On Hepatic Dysfunction.

(Transplant Proc , 1997; 29 (7): 2939)

IV- Trends

Ring III

- **Conversion from CsA to Neoral.**

- 400 patients:

GI : 300 patients had normal LFT.

GII : 100 patients had liver dysfunction.

(Mansoura Team, Transplant Proc , 1997; 29 (7): 2939)

IV- Trends

Ring III

- **The non hepatic group showed comparable parameters before and after conversion.**
- **The CsA dose reduction was:**
  - **16% in hepatic group.**
  - **10% in non hepatic group.**

(Mansoura Team, Transplant Proc, 1997; 29 (7): 2939)

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IV- Trends

Ring IV

Coadministration Of Ketoconazole To Cyclosporine Treated Kidney Transplant Recipients: Prospective Randomized Study : 10 Years Results.

(Transplantation, 2004; 77 (9): 1371)

IV- Trends

Ring IV

- **Recipients on P+ CsA + Aza.**
- **Prospective randomized trial:**

  GI : Keto (50 patients).

  GII : Control (50 patients).
- **Ten years follow up period.**

(Mansoura Team, Transplantation, 2004; 77 (9): 1371)

IV- Trends

Ring IV

- **Similar : Hepatotoxicity.**

  : Metabolic complications.

- **Control group :**

  - Frequent AR (27% Vs 22%, P: 0.27).

  - Poor response to antirejection therapy.

  - More fungal infection (60% Vs 6.6%, P: 0.001).

  - More IFTA (46% Vs 11%, P: 0.001).

(Mansoura Team, Transplantation, 2004; 77 (9): 1371)

IV- Trends

Ring IV

- **Low dose keto to CsA treated recipients:**
  - **Saves cost.**
  - **Favorable:**
    - **Fungal skin infection.**
    - **Chronic graft nephropathy.**
- **Recent ketoconazole awareness.**

(Mansoura Team, Transplantation, 2004; 77 (9): 1371)

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J Nephrol, 2003

IV- Trends

Ring V

Rescue Immunosuppressive Therapy In Living Related Renal Allotransplant: A Long Term Prospective Randomized Evaluation.

(Exp Clin Transplant, 2008; 6(1): 48)

IV- Trends

Ring V

Rescue Options

Shift from Aza to MPA

OR

Shift from CsA to Tac

IV- Trends and Trials

Ring V

- ***MPA:***
  - **Salvage for patients suffered from creeping creatinine.**
  - **Shift to MPA was associated with improved liver functions in patients suffering from hepatic dysfunction.**

(Mansoura Team, Exp Clin Transplant, 2008; 6(1): 48)

IV- Trends

Ring V

- ***Tacrolimus:***
  - **Potent rescue therapy.**
  - **Indicators for successful rescue :**
    - **Time to conversion.**
    - **S. Creatinine at conversion.**
  - **Good option in cases suffered from CsA adverse reactions.**

(Mansoura Team, Exp Clin Transplant, 2008; 6(1): 48)

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IV- Trends

Ring VI

INDUCTION THERAPY

A. Basiliximab

B. Daclizumab

C. Bolus ATG

D. Alentuzumab

IV- Trends

Ring VI A

Basiliximab Reduces The Incidence Of Acute Cellular Rejection In Live Related Donor Kidney Transplantation: Prospective Randomized Trial.

- ***At 3 years : J Nephrol, 2003; 16 (3): 393***
- ***At 5 years : Am J Nephrol, 2005; 25(3): 221***
- ***At 10 years : Exp Clin Transplant, 2011; 9(4): 247***

IV- Trends and Trials

Ring VI B

Daclizumab Reduces The Incidence Of Acute Cellular Rejection In Live Related Kidney Transplantation, A Single Centre Experience.

(Int Urol Nethrol, 2007; 39: 317)

IV- Trends and Trials

Ring VI C

Comparative Analysis Of Single Dose Bolus Antithymocyte Globulin Among Living Donor Renal Transplantation.

(Int Urol Nethrol, 2008; 40: 515)

IV- Trends

Ring VI D

Alemtuzumab Preconditioning Allows Steroid-calcineurin Inhibitor-free Regimen in Live-donor Kidney Transplant

Ayman F. Refaie,[1] Khaled M. Mahmoud,[1] Amani M. Ismail,[2] Hussein A. Sheashaa,[1] Ahmed I. Kamal,[1] Mohamed A. Ghoneim[3]

Abstract

Objectives: This prospective study was designed to develop a steroid and calcineurin inhibitor-free regimen for kidney transplants using alemtuzumab. *Materials and Methods:* A single dose of

Phase 2: Five patients developed successfully treated borderline changes with no antibody-mediated rejection. Mean serum creatinine was 114.9 ± 17.7 μmol/L. Currently, 17 patients are steroid-free and 15 of them are calcineurin inhibitor-free as well. In this phase, only 1 patient died with a

Experimental and Clinical Transplantation (2011) 5: 295-301

IV- Trends

Ring VI

❑ Conclusion:

- **Prophylactic induction is well tolerated and significantly reduces the incidence of acute rejection episodes after living donor renal transplantation.**
- **Up to 10 years follow up no impact on patients and graft survival was noticed.**

(Int Urol Nephrol, 2007 ; 39: 317)

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IV- Trends

Ring VII

Comparison Of mTOR With Low-Dose Tacrolimus Versus mTOR-Based Calcineurin Inhibitor-Free Regimen In Live Donors Renal Transplantation.

- ***At 2 years:*** ***Am J Transplant. 2005; 5 (10): 2531.***
- ***At 5 years:*** ***JASN, 2008; 19(6): 1225.***
- ***At 10 years:*** ***In press.***

IV- Trends and Trials

Ring VII

Prospective Randomized Trial

Basiliximab Induction

mTOR Based

Steroids

Randomization

CNI minimization → **Low dose Tac** → **GI**

CNI avoidance → **Full dose MPA** → **GII**

IV- Trends and Trials

Ring VII

- ***Results at 5 years:***
  - **Better graft function among CNI free.**
  - **No difference in patient and graft survival.**
  - **Less changes in primary immunosuppression in CNI free (20% Vs 53%, P=0.001).**

(Mansoura Team, J Am Soc Nephrol, 2008; 19(6): 1225)

IV- Trends

Ring VII

- *Results at 10 years:*

	Tac	MPA	P. value
* Mean follow up (years):	8.49±3.33	9.04 ±2.66	0.295
** Secondary IS*	*45 (69.2%)*	*22 (32.8%)*	*0.000*

(Mansoura Team, In Press)

IV- Trends

Ring VII

- *Results at 10 years:*

Results at 10 years	Tac	MPA	P value
Rapa dose (mg/day)	1.9479	1.9091	NS
Rapa level (ng/ml)	9.4680	10.2000	NS
FK dose (mg/day)	2.4516		
FK level (ng/ml)	5.4607		
MMF dose (gm/day)		1.3542	

(Mansoura Team, In Press)

IV- Trends

Ring VII

- ***Results at 10 years:***

Results at 10 years	Tac	MPA
Hb (gm%)	12.9816	12.6709
WBC (cmm)	9.6449	8.6727
Platelets (cmm)	2.3816E2	2.4805E2
Bilirubin (mg%)	0.7044	0.7164
SGPT (IU/L)	31.9535	28.9036
SGOT (IU/L)	30.4651	29.8036
Cholesterol (mg%)	178	192

(Mansoura Team, In Press)

IV- Trends

Ring VII

- *Results at 10 years:*

Adverse Events	Tac	MPA	P value
Hypertension	30(63.8%)	41(80.3%)	0.127
Diabetes Mellitus	19 (40.4%)	15 (29.4%)	0.252
Chronic IFTA	17(36.1%)	14(27.4%)	
Mild	11	11	0.456
Moderate	6	3	
Proteinuria:	14 (29.7%)	18 (35.2%)	
< 1 gm/day	5	8	0.750
1-3 gm/day	7	7	
≥ 3gm/day	2	3	

(Mansoura Team, In Press)

IV- Trends

Ring VII

- *Results at 10 years:*

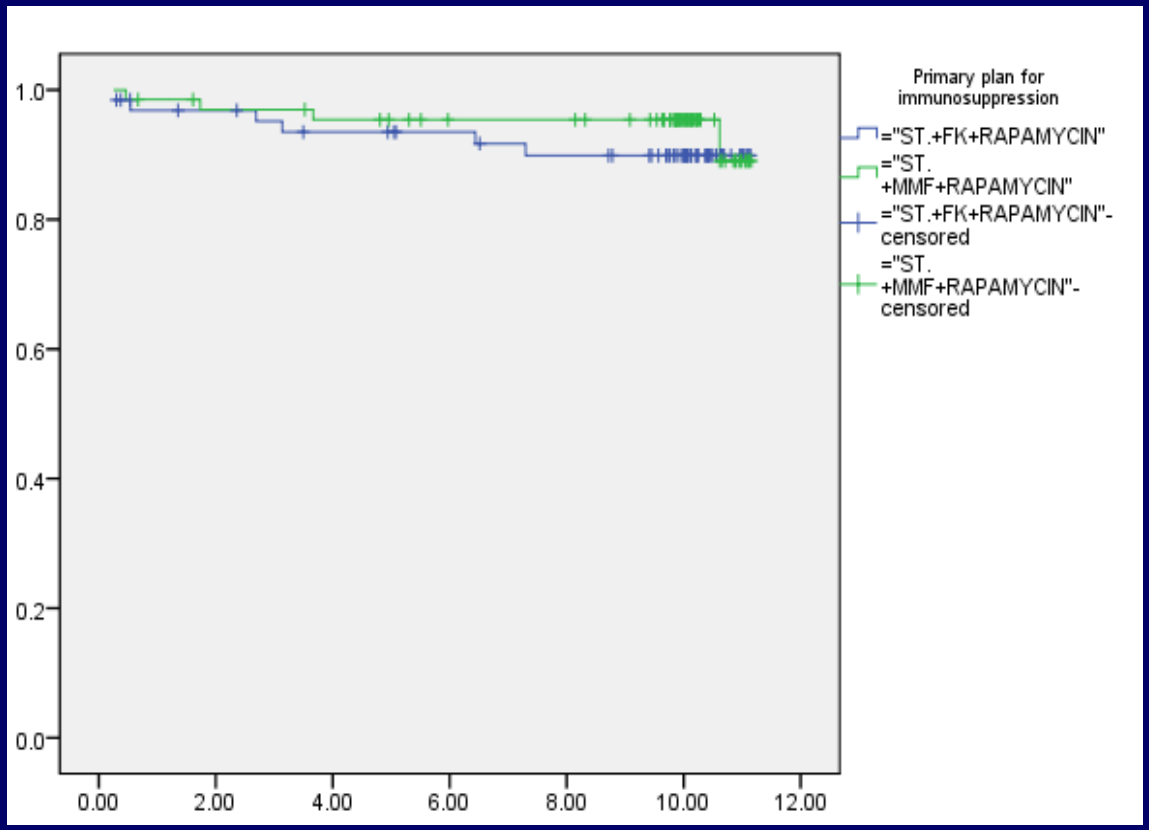
Condition at last follow up:	Tac	MPA	P. value
- Living with functioning graft	47 (72.3%)	51 (76.1%)	
- Died with functioning graft	6 (9.2%)	1 (1.5%)	0.082
- Living on dialysis	12 (18.4%)	12 (17.9%)	
- Died on dialysis	--	3 (4.5%)	

(Mansoura Team, In Press)

IV- Trends

Ring VII

- *Results at 10 years:*



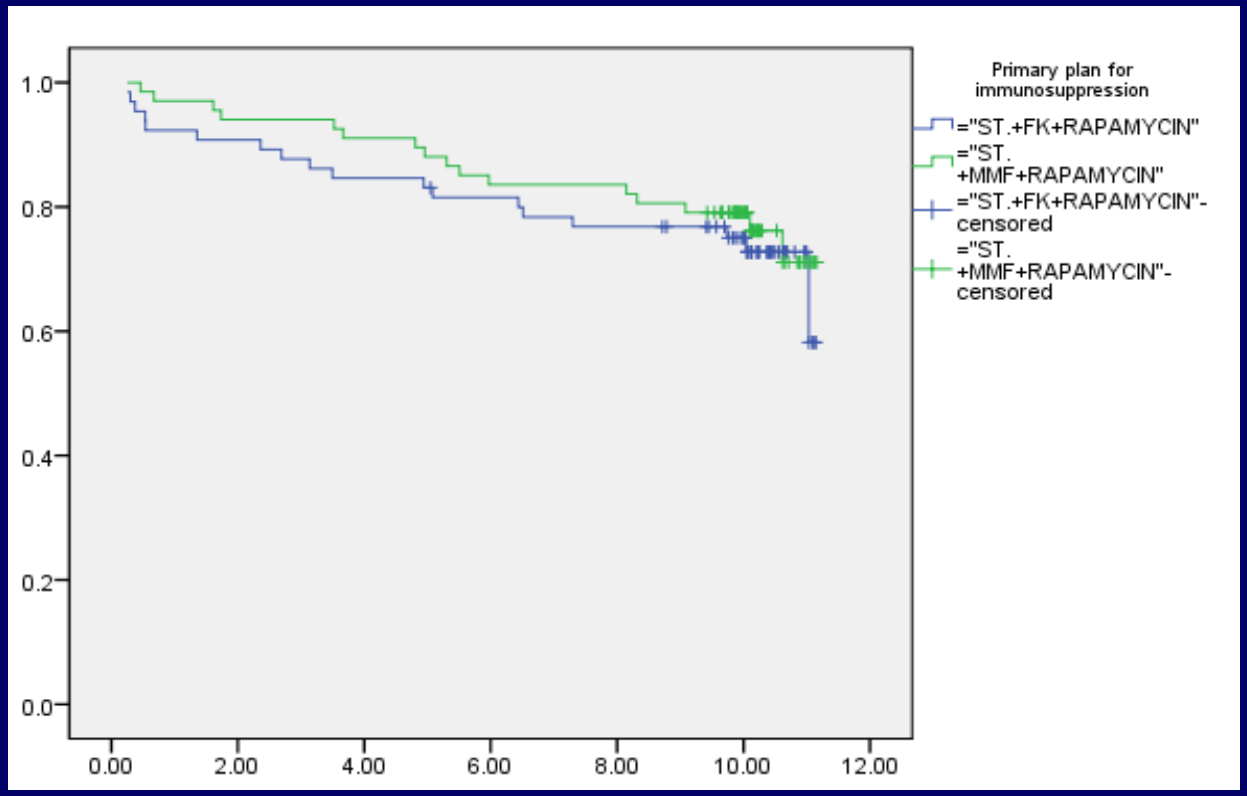
Observation period (Y)

(Mansoura Team, In Press)

IV- Trends

Ring VII

- ***Results at 10 years:***



Observation period (Y)

(Mansoura Team, In Press)

IV- Trends

Ring VII

- **Conclusion:**
  - **CNI free regimen (SIR + MMF + P) after induction therapy has proven to be both safe and effective.**
  - **To the best of our knowledge this study is the longest term prospective randomized study for SIR based therapy among living donor renal transplants.**

(Mansoura Team, In Press)

Immunosupperssion Rings of the chain

Conventional Vs Cyclosporin
RING I
AM J Nephrol, 13, 437: 1993

Transform
RING X
?

Avoidance
RING IX
In Press

Triple Vs Conventional
RING II
Transplant Proc., 25: 2243: 1993

Steroid Free
RING VIII
Exp Clin Tx, 5:673, 2009

Cyclosporine Neoral
RING III
Transplant Proc., 29(7): 2939: 1997

mTOR
RING VII
JASN, 19:1225, 2008

Keto Vs non Ketoconazole
RING IV
Transplant Proc., 26(6): 316: 1994

Rescue therapy: FK and MMF
RING V
Exp Clin Tx, 6: 48, 2008

Induction therapy With simulect
RING VI
J Nephrol, 2003

IV- Trends

Ring VIII

Steroid Avoidance In Low Risk Recipients Of Renal Allograft Is Feasible, Safe And Carries Fewer Morbidities.

(Exp Clin Transplant, 2007; 5(2): 673)

IV- Trends

Ring VIII

- **100 patients:**

  All : Simulect + Tac+ MPA.

  GI : steroids for 3 days only.

  GII : Maintenance steroids.

- **Median follow up was 12 M.**

(Mansoura Team, Exp Clin Transplant, 2007; 5(2): 673)

IV- Trends

Ring VIII

- **Patient and graft survival rates were 100%.**
- **Comparable S. Creatinine values, AR episodes and CADI score of one year protocol biopsy.**
- **Among Steroid Free Group:**
  - **Less DM (4% Vs 16%, P: 0.037).**
  - **Less weight gain (6% Vs 15%, P: 0.001).**
  - **Less hypertension (4% Vs 24%, P: 0.009).**

(Mansoura Team, Exp Clin Transplant, 2007; 5(2): 673)

IV- Trends

Ring VIII

- *Results at 10 years:*

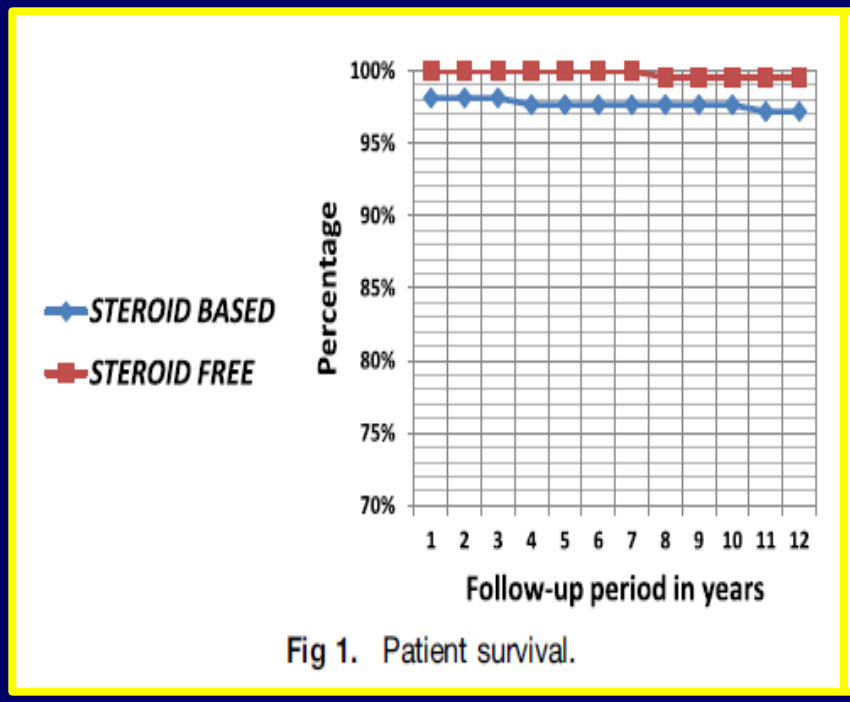


Fig 1. Patient survival.

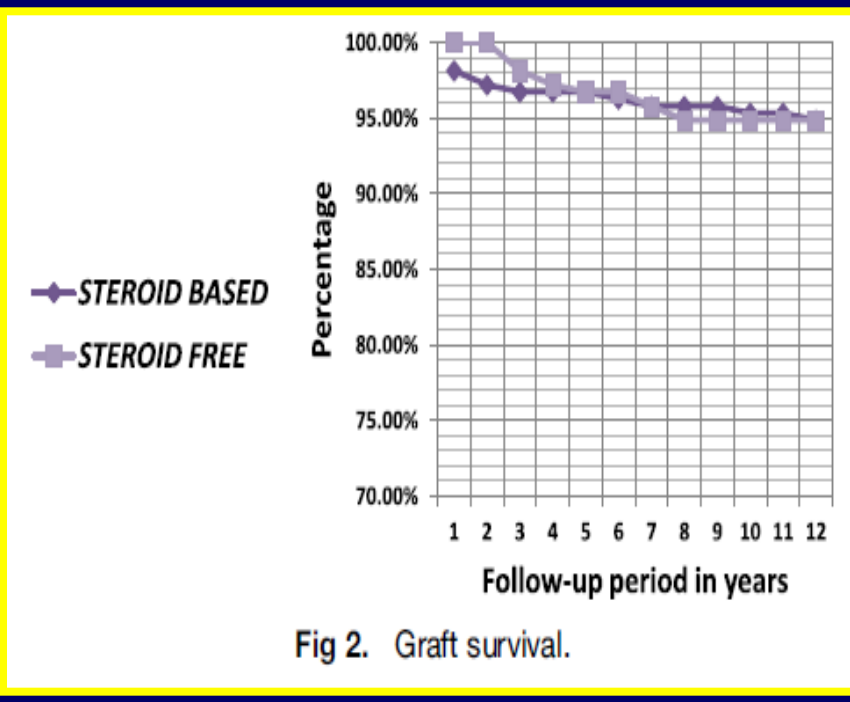


Fig 2. Graft survival.

(Mansoura Team, Transplant Proc, 2015; 47, 1099)

IV- Trends

Ring VIII

- ***Results at 10 years:***

- Among low-immunological-risk recipients of living-donor renal transplants, steroid avoidance was:

- **Feasible, safe, and had less morbidity.**
- **Associated with a lower total cost despite comparable immunosuppression cost, which was attributed to the lower cost of associated morbidities.**

(Mansoura Team, Transplant Proc, 2015; 47, 1099)

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RING V
Exp Clin Tx, 6: 48, 2008

Induction therapy With simulect
RING VI
J Nephrol, 2003

IV- Trends

Ring IX

The Efficacy Of CNI Free, Steroid Free Immunosuppression Protocol And Its Role In Tolerance Induction Using mTOR Inhibitor: Prospective, Randomized, Controlled Study.

IV- Trends

Ring IX

- **Comparing the efficacy of CNI-free steroid free protocol against CNI-based regimen.**
- **Assessing the role of mTOR inhibitors "Rapamycin" in induction of tolerance.**

(In Progress)

IV- Trends

Ring IX

- ***Exclusion criteria :***

  - Re-transplanted.

  - PRA > 10% class I and II.

  - BMI > 32 kg/m2.

  - Historically positive cross-match.

(In Progress)

IV- Trends

Ring IX

- ***Avoidance Study:***
  - **Basiliximab at day 0, 4.**
  - **Steroids for 1 week.**
  - **Tacrolimus for 3 months.**
  - **Randomization:**
    - **GI: continue Tac.**
    - **GII: convert to mTOR .**

(In Progress)

IV- Trends

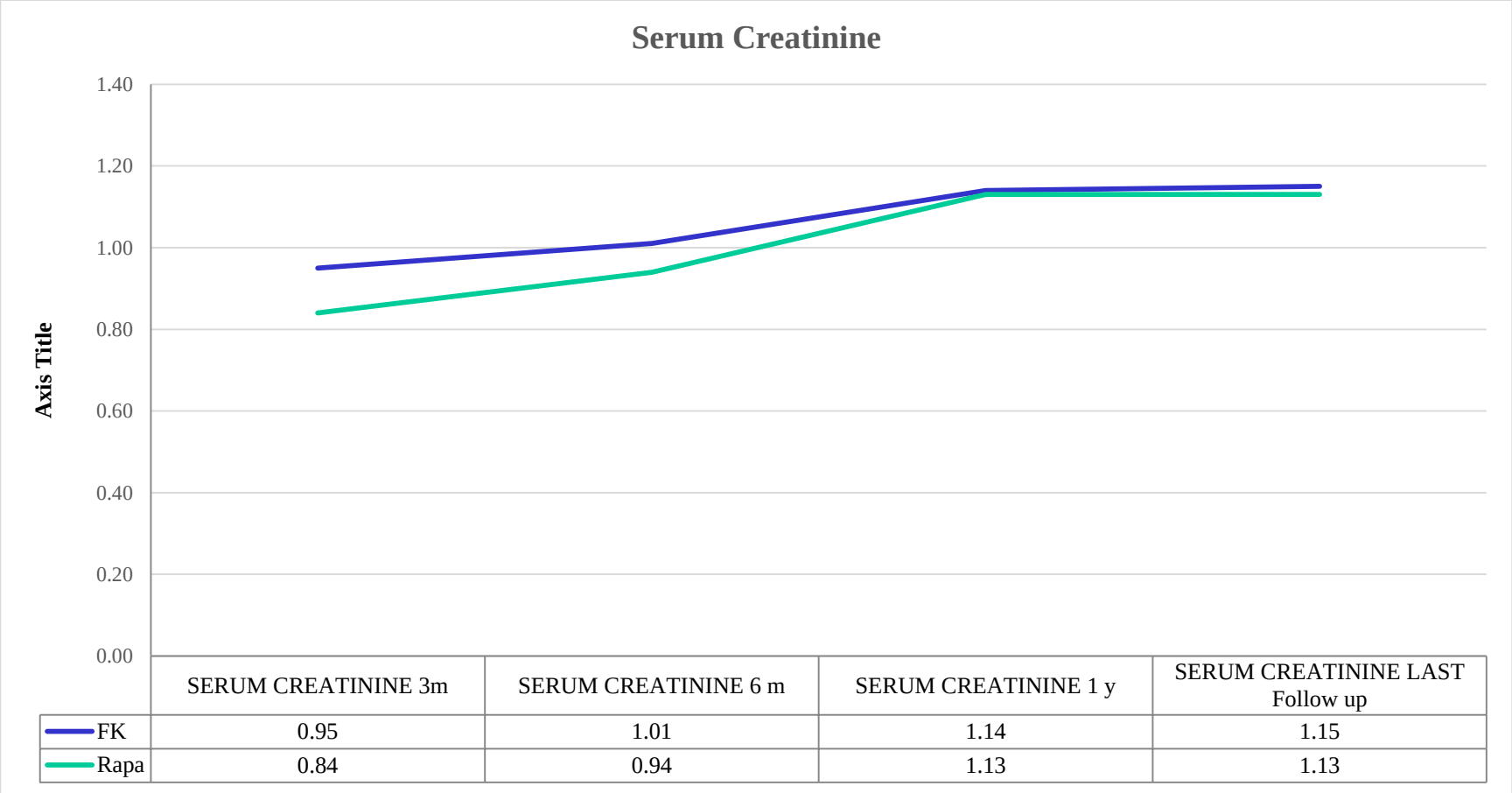
Ring IX

- ***Immunologic work up:***
  - **T-reg cells ($CD4^+$, $CD25^+$, $FoxP3^+$).**
- ***Histopathologic work up:***
  - **Implantation biopsy.**
  - **Randomization biopsy.**
  - **Protocol biopsy.**

(In Progress)

IV- Trends

Ring IX

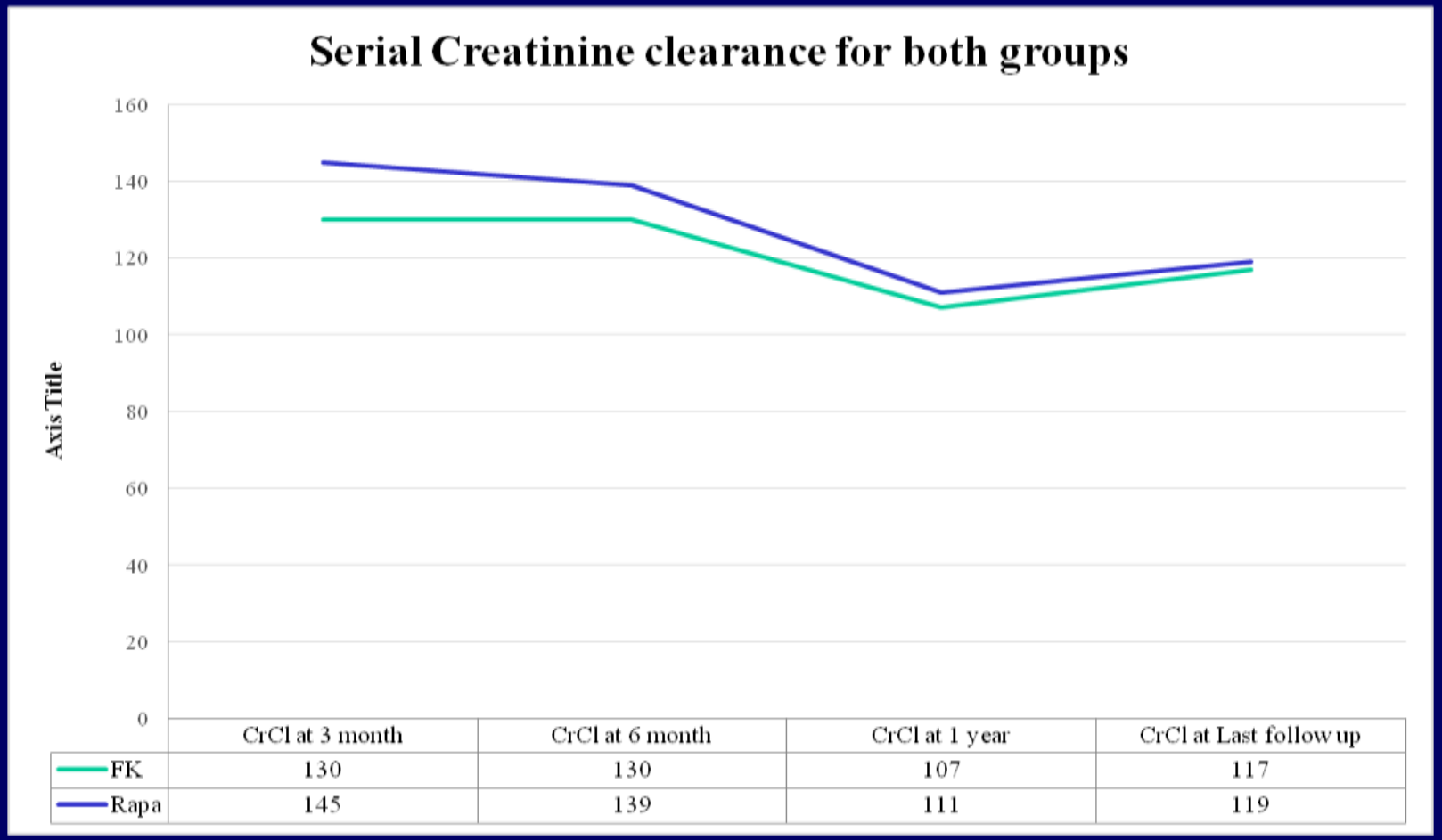


	SERUM CREATININE 3m	SERUM CREATININE 6 m	SERUM CREATININE 1 y	SERUM CREATININE LAST Follow up
FK	0.95	1.01	1.14	1.15
Rapa	0.84	0.94	1.13	1.13

(In Progress)

IV- Trends

Ring IX



	CrCl at 3 month	CrCl at 6 month	CrCl at 1 year	CrCl at Last follow up
FK	130	130	107	117
Rapa	145	139	111	119

(In Progress)

IV- Trends

Ring IX

At 12 month	(Tac group)	(SIR group)	P value
S cholesterol (mg/dl)	155.5±37.4 (97- 213)	211.45± 36.7 (154-279)	0.012
Hemoglobin (gm/dl)	11.25±1.5 (9 -13)	10.9±1.5 (9 - 13)	0.37
Fasting plasma glucose (mg/dl)	98±10.8 (80- 107)	92± 12.88 (82- 113)	0.5
White cell count (/Cmm)	5.2± 2.2 (4.5-9.5)	4.8±2.3 (4-8.9)	0.38
Platelet count (/Cmm)	205± 45 (180-285)	185±35 (172-280)	0.3

(In Progress)

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Exp Clin Tx, 5:673, 2009

RING IX
Minimization
In Press

RING X
Transform
?

IV- Trends

Ring X

Transform: A Novel Study Design To Evaluate The Effect Of Everolimus On Long- Term Outcomes After Kidney Transplantation.

(Open Access Journal of Clinical Trials, 2014;6: 45)

IV- Trends

Ring X

- **Started June, 4th 2014.**
- **Completed July, 28th 2015.**
- **25 patients:**
  - **EVR arm 15 patients.**
  - **Control arm 10 patients.**

(Mansoura Team, Transform Study)

Immunosuppression

V. At The End

V. At The End

- **Start combination of IS before or at time of renal transplantation [1A].**
- **Induction therapy [1A].**
    a) **First line IL2R A [1B].**
    b) **ATG for high risk [2B].**
- **Maintenance IS: CNI + antiproliferative ± P [1B].**

(KDIGO, Am J Transplant,

V. At The End

- **MMF as first line antiproliferative [2B].**
- **mTOR use after graft functions [1B].**
- **Lowest doses IS after 2-4 M if no AR [2C].**
- **Continue CNI rather than withdrawan [2B].**
- **Continue P rather than withdrawn [2C].**
- **In CNI toxicity reduce, withdraw, replace CNI [2C].**
- **If GFR> 40 ml/min, proteinuria < 500 mg/d, replace to mTOR [2D].**

(KDIGO, Am J Transplant, 2009)

V. At The End

No IS = **Optimal IS** = **Tolerance**

Effective (prevent AR)

↓

Lower rates of SCR

↓

Reserve renal function

↓

Preserve histology

↓

Non nephrotoxic

↓

Acceptable adverse reactions

↓

Selective action

↓

Low CAN/ IFTA

V. At The End

- **Novel immunosuppressive agents over last two decades**

Beside

- **Improvement of diagnostic tools for early detection of antibody mediated injury**

Allow

- **Better match the immunosuppression needs**

Potential for

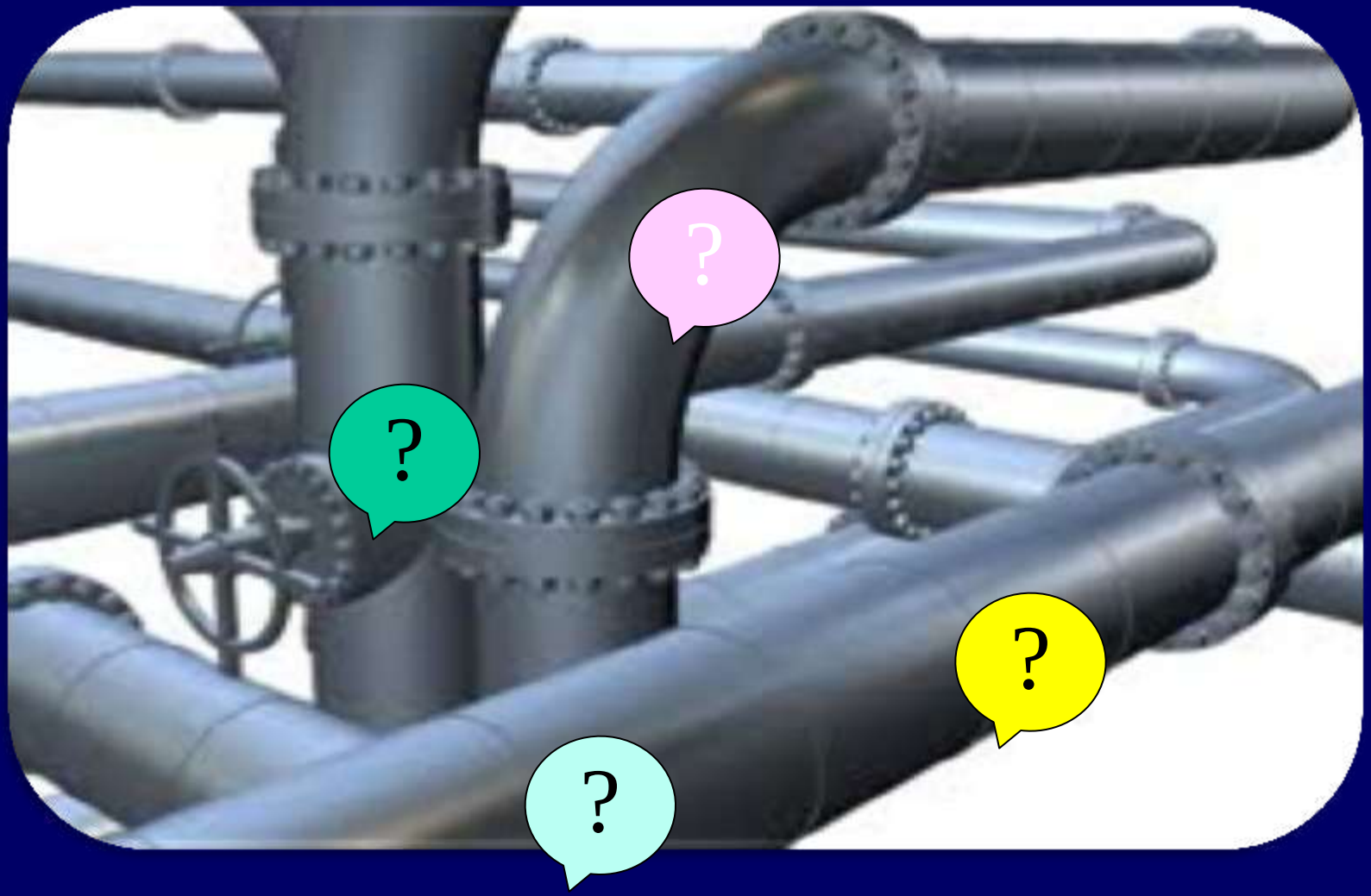
- **Personalized medicine**

One size did not fit all

(Zsom et al., WJT, 2015)

V. At The End

* Pipelines



V. At The End

* Tailoring of Immunosuppression

V. At The End

Final Chapter

↓

2016

↓

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Immunosuppression